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(54) A BLOOD GLUCOSE LEVEL MONITORING-ALARM SYSTEM AND METHOD THEREOR

(71) We, WHITTAKER CORPORATION, a Corporation of the State of California, U.S.A. of 10880 Wilshire Boulevard, Los Angeles, California 90024, U.S.A. do hereby declare the invention for which we pray that a Patent may be granted to us and the method by which it is to be performed to be particularly described in and by the following statement:—

This invention relates to glucose monitoring systems in general, and more particularly to an implantable glucose monitor and alarm system for use in the measurement and control of blood glucose levels in diabetics.

It is important for the diabetic patient to maintain normal or near normal blood glucose levels throughout the day. These levels can be obtained through appropriate diets, insulin injections and exercise patterns. However, in order to avoid over or under compensation, it is desirable for the diabetic patient to know his blood glucose level in order to take appropriate compensatory action.

Unfortunately, at the present time, continuous blood glucose measurements can only be performed outside the body. Basically, such measurements involve the following operations: using a double lumen cannula, blood is continuously drained from a vein, mixed with heparin solution and then sent to a dialyasis cell. The glucose which has been dialyzed out is allowed to react with the appropriate amount of reagent such as glucose oxidase, glucose oxidase-HVA-peroxidase mixture, or potassium ferricyanide. The glucose concentration is then obtained by either spectropolarimetry, fluorescence or colorimetry depending upon the reagent used. Blood glucose measurements using this system are obviously time consuming and inconvenient with respect to an ambulatory diabetic patient.

According to the present invention there is provided a method for monitoring blood glucose levels comprising the steps of:—

(1) exposing a glucose diffusion-limited fuel cell as herein defined to the body fluid of a living body in such a way that a change takes place in the fuel cell in a selected characteristic that varies in a manner proportional to the blood glucose level and

(2) measuring the change in the selected characteristic or in a signal derived from the selected characteristic in order to obtain a measurement of the blood glucose level.

The selected characteristic is preferably the output current generated by the fuel cell which is proportional to the blood glucose level, the output current being converted into an electrical signal which varies in accordance with the magnitude of the output current.

Other selected characteristics which may be measured include:—

1. the rate of potential rise in a cell on charging since the rate of charging varies with the glucose level
2. the temperature rise due to glucose oxidation
3. the change in pH value as a result of the formation of gluconic acid
4. the reduction of oxygen tension as a result of O_2 consumption.

It is accordingly, a general object of the present invention to provide a glucose monitor and alarm system for the measurement and control of blood glucose levels of diabetics and to provide a compact, implantable, self-sustained sensor-telemetering system which is capable of providing measurement of blood glucose concentrations.

The present invention includes a method for monitoring blood glucose levels comprising the steps of:

(1) exposing a glucose diffusion-limited

fuel cell as herein defined to the body fluid of a living body and

(2) converting the output current generated by said fuel cell into an electrical signal having a characteristic which varies in accordance with the magnitude of the output current, said output current magnitude being proportional to the blood glucose level in said living body. An alarm signal may be actuated whenever the said electrical signal characteristic departs from a predetermined condition.

The invention also includes a glucose diffusion-limited fuel cell as herein defined comprising:—

(1) at least one permeable membrane which defines a chamber and which is permeable to body water, oxygen and glucose,

(2) first and second, spaced, catalyst-coated electrodes positioned within the chamber and comprising, respectively, a cathode electrode, and an anode electrode for said fuel cell,

(3) means for glucose diffusion limiting the said fuel cell,

(4) a load resistance electrically interconnected with the cathode and the anode electrodes and,

(5) an electrolyte interposed between the said first and second electrodes.

Preferably the anode has a smaller surface area than the cathode and the anode preferably includes means for impeding the diffusion of glucose. The cathode may include means for impeding the diffusion of glucose while permitting substantially free passage to water, ions and oxygen whereby the cathode serves as an oxygen electrode. The cathode and anode may comprise dissimilar materials.

The invention also includes as in vivo blood glucose level monitoring system comprising:

(1) a glucose diffusion-limited fuel cell as herein defined adapted for implantation in a living body, and

(2) means for converting the output current generated by the fuel cell when implanted in a living body, into an electrical signal having a characteristic which varies in accordance with the magnitude of the output current, the said output current magnitude being a function of the blood glucose level in the living body. In more detail the system may comprise

(1) means adapted when the system is in operation for generating a glucose valve actuation signal whenever the electrical signal characteristic departs in one direction from the said predetermined condition and an insulin valve actuation signal whenever the said characteristic departs in the opposite direction from the said predetermined condition;

(2) first fluid valve means adapted to respond to the glucose valve actuation signal,

(3) second fluid valve means adapted to respond to the insulin valve actuation signal,

(4) a source of glucose adapted to be fluidly coupled through the first valve means to the living body; and

(5) a source of insulin adapted to be fluidly coupled through the second valve means to the living body.

These objects and features and other objects and features of the present invention will best be understood from a detailed description of a preferred embodiment thereof, selected for purposes of illustration, and shown in the accompanying drawings in which:

Figure 1 is a diagrammatic view in partial block form showing the glucose diffusion-limited fuel cell and telemetering circuitry;

Figure 2 is a polarization curve for a typical fuel cell;

Figure 3 is a block diagram of the electrical circuitry of the blood glucose monitoring system; and,

Figure 4 is a diagrammatic view in partial block form showing the alarm and control circuitry and the equipment for maintaining a predetermined blood glucose level in a living body.

The present invention utilizes an implantable fuel cell, indicated generally by the reference numeral 10 in Figure 1 to obtain an electrical indication of the blood glucose level in a living body. Before discussing the fuel cell 10 in detail, it will be helpful to briefly review the characteristics of a fuel cell with special emphasis on the requirements for an in vivo fuel cell.

A fuel cell is an electrochemical energy conversion device composed of a nonconsumable anode and cathode, an electrolyte, and suitable arrangements and controls for maintaining selective environments for a fuel anode and an oxidant cathode. Fundamentally, any oxidation-reduction reaction is a fuel cell candidate; the practicality, however, depends primarily on the reaction rate. The most efficient and highly refined fuel cell system known to date is the human body which uses enzymes to catalyze the oxidation of food (fuel) in an electrolyte (body or cell fluid), producing energy—some of which is electrical. By providing different kinds of active catalysts such as platinum, palladium and nickel, certain carbohydrates (glucose, for instance), plentiful in the human body, which contain aldehyde (or similar groups) can be activated at low temperatures in a fuel cell to generate electricity. A metallic catalyst impregnated on the electrode surface will promote the reaction of glucose with water, absorbing electrons and releasing hydrogen ions. This fuel rich electrode constitutes, therefore, the anode of the fuel cell. If, in addition, an identical catalyst-coated electrode supplied with oxygen is introduced

into the same electrolyte solution, OH ions will be released and a potential difference can be detected across these electrodes. The later oxygen rich electrode is naturally the cathode of the fuel cell, and the generated voltage is essentially a constant, characteristic of the fuel used, while the current flowing in leads connecting the electrodes is closely related to the fuel concentration near the anode. Based on this principle, an implanted fuel cell can be considered for the measurement of glucose level of body fluid or blood.

However, simply implanting two catalyst-coated electrodes into the body will not yield any electrical output. Provision must be made for alteration of conditions near the electrodes and this can be accomplished by placing the electrodes at different locations within the body to achieve a selective electrode environment. Although electrical energy can thus be obtained, such a system cannot be used to measure glucose concentration. The transport of ions within the porous electrode and electrolyte, will be rate limiting, and the internal cell resistance will be high. The present invention eliminates this problem by utilizing a glucose diffusion-limited fuel cell as herein defined in which the diffusion of glucose is restricted.

The basic construction of the glucose fuel cell sensor 10 and its associated circuitry are shown in Figure 1. The fuel cell 10 is principally a controlled-diffusion device which employs artificial membranes and coating materials of varying thickness and characteristics to vary the diffusion rate of glucose relative to that of oxygen on the basis of molecular size, mobility, or solubility in the membrane and coating materials.

The fuel cell 10 and its associated microcircuitry 12 are encased in an external membrane 14 constructed of newly-developed inert high dialysise rate membrane materials (such as those developed by Union Carbide, G.E., and DuPont) which permit substantially free transmission of oxygen, glucose and similar size compounds but impede the diffusion of large, more complex macromolecules, such as proteins, polysaccharides, cholesterols, etc. The membrane 14 defines a chamber 16 within which are positioned two spaced transition metal catalyst coated electrodes 18 and 20 that comprise an anode electrode and a cathode electrode, respectively. The anodic and cathodic reactions are:

$$C_6H_{12}O_6\ (\text{Glucose}) + H_2O \xrightarrow{Pt} C_6H_{12}O_7\ (\text{Gluconic acid}) + 2H^+ + 2e\ (\text{Anodic}) \quad (1)$$

and

$$1/2O_2 + H_2O + 2e \xrightarrow{Pt} 2OH^-\ (\text{Cathodic}) \quad (2)$$

and the overall reaction is

$$1/2O_2 + C_6H_{12}O_6 \longrightarrow C_6H_{12}O_7\ (\text{Overall}) \quad (3)$$

The cathode which has a larger surface area is covered with a thin layer of an artificial membrane 22 which allows substantially free passage of water, oxygen, etc., but strongly resists the diffusion of glucose so that it serves as an oxygen electrode. The smaller anode 18 is covered with a relatively thick layer of porous plastic material 24 which impedes the diffusion of glucose and protects the catalyst (platinum) from poisoning and from the physical, chemical, and biological harassment of the body. The body fluid within the membrane-encased chamber 16 constitutes an electrolyte 26 for the fuel cell. Alternatively, an anion, a cation exchange membrane, or a combination of the two ion exchange membranes can be interposed directly between the fuel and the oxygen electrodes to serve as a solid electrolyte as well as a partition for the fuel and the oxygen half cells. When both ion exchange membranes are simultaneously displaced in parallel, cell performance is generally improved, noise and signal drift reduced, and problems associated with water accumulation or starvation in the oxygen half cell can be avoided. One mode of operation is therefore to coat the electrodes without using separators, another mode of operation is to use separators and it is also possible to use both separators and coated electrodes.

Preferably, a platinized anode is used which catalyzes the dehydrogenation of the aldehyde group of the glucose molecules that have diffused through the anode coating 24 and impinged upon the platinum surface. This electrode is therefore the glucose or the fuel electrode. Because the cathode or oxygen electrode 20 is larger, and because oxygen is lighter and smaller and therefore has a larger diffusion coefficient, and further because the diffusion of glucose to the anode is impeded, the rate of oxygen molecules arriving at the cathode can be arranged in such a way that it is always larger than the rate of glucose impingement on the anode surface. As a result, the current that can be drawn from the fuel cell 10 is proportional to the diffusion or arrival rate of glucose molecules and hence to the concentration of glucose in the body fluid, and, in turn, to the concentration of glucose in blood.

A glucose diffusion-limited fuel cell, means a cell involving a direct electrode reaction, an ample supply of glucose and water in which an ample supply of oxygen is maintained and the following condition is satisfied at all times and at all possible glucose levels:

$$\frac{D_{oc}N_oA_c}{\delta_c} > \frac{\Omega}{2}\frac{D_{ga}N_gA_a}{\delta_a} \quad (4)$$

where Ω is the effective steric factor of the anodic reaction, A_a is the area of electrode a, N_g the number density of species g, D_{ga} the diffusion coefficient for transport of species g through the surface layer of electrode a and δ_a the thickness of surface layer of electrode a. Subscripts a, c, g, and o pertain to the anode 18, the cathode 20 and the glucose and oxygen, respectively.

The standard open circuit voltage of the glucose fuel cell is approximately 0.85 volt and it is a constant, essentially characteristic of the overall reaction expressed by Eq. (3). This voltage can be evaluated based on known electrochemical constants and is approximately equal to the sum of the theoretical E.M.F. of the participating anodic and cathodic reactions. The electrodes must be arranged in close proximity to one another so that the diffusion of electrode ionic products H^+ and OH^- is not the rate limiting process in the generation of electrical power.

The terminal voltage of a fuel cell depends on its current, and a typical voltage versus current commonly referred to as the polarization curve is given in Figure 2. Since the glucose concentration is only proportional to the output current that can be sustained by the fuel cell, load resistance 28 must be very small so that the current will correspond to the value at the tail of the polarization curve (i.e., in the concentration polarization regime). Typically the resistance of load resistor 28 is in the range of 0 to 10 ohms.

Although a platinum black anode is preferred for use in the glucose fuel cell 10, other Group VIII transition metals can also function satisfactorily as fuel (glucose) electrode catalysts. These metals (palladium, nickel, platinum) are active catalysts for heterogeneous hydrogenation-dehydrogenation reactions. Their catalytic properties can be explained by their electron receiving capacity and by the fact that they are capable of forming covalent bonds with fuels through the metal d-band during the electrode reaction. This also explains why nontransition group metals, whose d-orbitals are completely filled, are not catalytic. The limited catalytic activity of the metals other than Group VIII, notably the Group I_B metals (gold, silver, copper, etc.) is attributed to a d-s promotion that gives them d-orbital vacancies.

While the selection of (anodic) fuel electrode catalysts is relatively limited, the choice for (cathodic) oxygen electrode catalysts is considerably broader. In contrast to their poor performance as fuel catalysts, the Group I_B metals and their oxides are at least as active oxygen catalysts as the Group VIII metals, except perhaps that the path of oxygen reduction is different. The reduction has been postulated as yielding (1) hydroxyl ions (Eq. 2) or (2) perhydroxyl ion and a hydroxyl ion,

$$O_2 + H_2O + 2e \rightarrow O_2H^- + OH^- \quad (5)$$

It has been established through electrochemical studies that the reduction on platinum proceeds according to Eq. (2) in both acid and alkaline electrolytes. For this reason, the use of platinum as oxygen electrode catalysts is favored for more efficient utilization of oxygen.

Finally, it is important to note that it may be more advantageous to employ metals (or metal oxides) such as gold, silver, etc. as the catode (oxygen electrode) catalyst to achieve asymmetry which is indispensible for generation of electric output. These materials are good oxygen electrode catalysts but poor glucose catalysts (relative to platinum, palladium and nickel). The necessary asymmetry or electrode selectivity can be achieved through one or all of the following schemes: (1) differential electrode area; (2) control of diffusion rates by different surface coatings; (3) dissimilar electrode materials.

Although the open circuit equilibrium cell potential is insensitive to the glucose concentration, the rate of charging generally varies with the glucose level. Hence, by periodically discharging the cell, the glucose concentration, can alternatively be determined by measuring the rate of potential rise. Other modes of operation of the fuel cell sensor include measurements of temperature rise due to glucose oxidation, the change in pH value as a result of the formation of gluconic acid, and the reduction of oxygen tension as a result of O_2 consumption, which may be caused by catalytic action of electrodes.

The implantable glucose requires non-autogenous materials for long-time subdermal contact with the human body. These materials must, therefore, be non-antagonistic to the environment into which they are placed. Recent advances in biomaterials research, motivated by the development of artificial kidney, lung, heart and other organs, have resulted in a number of new materials whose biological compatibility has clearly been demonstrated. These include "Silastic", silicone rubbers, "Teflon", (Registered Trade Mark), polyethylene, cellulose, semipermeable hollow fibers, collagens and etc. Since these materials can generally be synthesized into different forms with different porosity and selectivity, they are ideally suited for the present invention.

The output current from the fuel cell 10 is amplified by a current amplifier 30 which has a low input impedance and therefore measures the short circuit current which is

proportional to the glucose diffusion rate, which is in turn, proportional to the blood glucose concentration. The amplified output current is converted to a frequency by a current-to-frequency converter 32. The blood glucose level information now in frequency form, is transmitted by transmitter 34 to an external receiver 36.

The detailed circuitry employed in the implantable glucose sensor-monitor alarm system is shown in Figure 3. Looking at Figure 3, the output current from fuel cell glucose detector 10 is applied to the current amplifier 30. The amplified current output from amplifier 30 is used to charge a small integrating capacitor 38 to much higher voltages than normally are obtainable from the glucose cell sensor 10. The integrating capacitor 38 together with a low-power electronic device, such as a unijunction transistor 40 is used to provide short pulses in the range of 1 kilohertz. Since the unijunction transistor draws power only when it is switching, the power requirements for this circuit are quite low.

The frequency of oscillation of the UJT is directly proportional to the current from the glucose fuel cell sensor 10. By the use of a current-to-frequency converter technique, the blood glucose level information can be processed to a form which is much more readily transmitted to the external receiver 36. The output pulses of the UJT oscillator 40 are used to trigger a silicon control rectifier switch 42 to drive a resonant LC network 44 which is tuned to about 1 megahertz. The shock excited resonant circuit 44 generates bursts of 1 megahertz rf energy at at repetition rate of about 1 kilohertz. The output from the shock excited circuit 44 is directly coupled to an rf radiating plate 46.

The use of the 1 megahertz carrier extends the transmitting range outside of the body and it also simplifies the receiver tuning to reduce spurious signals. The repetition rate of the rf carrier contains the information with respect to the glucose concentration. The use of brief bursts of rf energy with a low duty cycle of about 10 percent or less reduces the average power requirements of the rf transmitter with a concomitant reduction in the required battery size or an extension of the battery life.

In its preferred form, the telemetering system of the present invention utilizes pulse-code modulation. However, it should be understood that the PCM mode is merely illustrative and that the other modulation modes can be employed to telemeter the blood glucose level information to an external receiver.

The repetition rate at normal glucose levels is chosen to be approximately 1 kilohertz with provision for a dynamic operating range of a factor ± 10. In this way, the UJT oscillator 40 is able to operate from 100 hertz up to 10 kilohertz with a nominal value of 1 kilohertz. These parameters permit telemetering of information about the glucose condition from a value of 1/10 the normal to 10 times the normal level.

The telemetering accuracy of this system is quite high. Under a worst case situation corresponding to 100 hertz, the reception of the signal for 1 second will be sufficient to give a reading with an accuracy of ± 1 count corresponding to an accuracy of $\pm 1\%$. The accuracy of the system at higher repetition rates is obviously much greater and is far greater than one really needs for the overall system. This provides a satisfactory margin of reserve while at the same time keeping the electronic system reliable and compact.

Since the glucose fuel cell 10 and associated telemetering components shown in Figure 3 are implanted in the body, it is desirable to provide external adjustment of the electronics within the telemetering system without requiring surgical techniques. This can be accomplished by the inclusion of a tiny adjustable potentiometer 48 to which is attached a small magnetic bar 50 which can be readily rotated by means of a permanent magnet (not shown) located outside of the body. By properly positioning the external permanent magnet and rotating it the required number of turns, it will be possible to adjust the multi-turn potentiometer 48 to change the calibration set points of the telemetering system. This can be done most conveniently in the gain-control portion of the current amplifier 30 as shown in Figure 3.

A variety of options are available with respect to supplying power to the electronic portion of the glucose monitoring system. Referring to Figure 3, power can be obtained from an internal battery 52. If desired, provision can be made for external recharging of the implanted battery by means of magnetic coupling through the skin. If this mode of operation is employed, a magnetically powered battery recharger, indicated generally by the reference numeral 54, is included within the implanted glucose monitor. Power for the battery recharger 54 is provided by magnetic coupling from an external electromagnet 56.

In the basic mode of operation where the current from the fuel cell sensor 10 is amplified by current amplifier 30, converted to a frequency by a UJT oscillator 40 and used to shock-excite a resonant LC circuit 44, the average power of the electronics is quite low in comparison to the peak rf power transmitted by the internal shock-excited oscillator. This is because the energy stored within a capacitor is periodically dumped into the shock-excited LC circuit 44 and flows for only a short time (e.g. for 10 or 20

microseconds). The duty cycle of this oscillator is low so that the average power is quite small compared to the peak power transmitted.

Assuming that the rf radiating plate 46 and the receiver 36 (Figure 4) normally will be separated by approximately 10 feet and that the normal range of a transmitter at milliwatt power levels is approximately 10 feet, it can be seen that the shock-excited oscillator 44 will have the desired 10 foot radiation range while requiring peak powers e.g. of 10 milliwatts or average powers e.g. of 1 milliwatt—even allowing for relatively low efficiency in a shock-excited oscillator. Since the power requirements of a uni-junction oscillator are negligible except during short periods of time when it acts as a current switch transferring the charge in the capacitor to the resonant LC network, the main power requirement for the system will be from the current amplifier 30. Using off-the-shelf integrated circuits, the current amplifier can be designed to have an average power requirement of about 5 milliwatts. It will, therefore, be appreciated that the information gathering, processing and transmitting electronics of the glucose monitoring system will require an average power of about 10 milliwatts, taking into account the appropriate duty cycles and a continuous transmission of the one kilohertz modulated carrier wave.

Further reduction in the average power requirements can be obtained by providing intermittent telemetering of the glucose level information. This is accomplished by including a relatively simple uni-junction, low-powered clock oscillator. The clock oscillator circuit comprises a fifteen minute UJT clock 60, a five second clock 62, a normally OFF flip-flop 64 and a FET switch 66. The clock oscillator turns on the measuring, amplifying and telemetering circuits once every fifteen minutes. If the telemetering system is turned on for a period of approximately 5 seconds during each fifteen minute interval, this corresponds to a duty cycle of one part in 180 and the average power requirement is reduced by a factor 180. Although there will be some minor increases in the power requirements due to the additional electronics, even if this doubled the average power requirements for the electronics, the overall savings will be at least a factor of 90, which is almost 100-fold reduction of power requirements of a 100-fold extension of the life of the battery 52, assuming that the shelf life of the battery is not the basic constraint.

Under certain circumstances, it may be desirable to provide a manual override control for the clock oscillator. This can be accomplished by providing a magnetically actuated reed relay 68 which bypasses the fifteen minute UJT clock 60 and actuates the normally OFF control flip-flop via clock 62. When FF 64 is in the ON condition, the output thereof biases FET switch 66 into conduction thereby applying power from battery 52 to the power bus 70.

Looking now at Figure 4, there is shown in diagrammatic and partial block form the external portion of the glucose monitoring-alarm system of the present invention. The radio frequency energy radiated by the implanted radiation plate 46 (Figure 3) is received by the external receiver 36. The modulation frequency is extracted from modulated rf carrier by extractor 72 and converted to a voltage by converter 74. The output voltage from converter 74 represents the blood glucose level in the monitored living body. This voltage is then inputted to a voltage comparator 76 which compares the blood glucose level input voltage with a voltage or a range of voltages which represent a normal or desired blood glucose concentration.

In the preferred embodiment, two adjustable voltage reference levels 78 and 80 also are inputted to the voltage comparator. These two reference voltages define the acceptable range for the voltage output from the converter 74. If the output voltage from the frequency-to-voltage converter (which represents the blood glucose concentration in the monitored living body) falls within the range of voltages defined by the two reference levels, no output is generated by the voltage comparator. Normally, the two voltage reference levels are selected to correspond to the points at which glucose or insulin must be supplied to the monitored living body in order to maintain a normal blood glucose level. For purposes of illustration, the relative voltage levels can be considered only in term of positvie voltages with the glucose voltage level being the most positive. Therefore, it can be seen that if the output voltage from the frequency-to-voltage converter 74 exceeds the glucose voltage reference level, the voltage comparator will produce a glucose output signal on lead 82. Conversely, if the voltage output from the converter falls below the insulin voltage reference level, the voltage comparator will produce an insulin output signal on lead 84. The output leads from voltage comparator 76 are inputted to an OR circuit 86 which in turn is connected to a suitable alarm means 88. Various types of alarm means can be employed including visual, audible, and/or a physical stimulus to the monitored living body. The alarm means will actuate whenever the output voltage from the frequency-to-voltage converter falls outside of the normal range of voltages established by the glucose and insulin refernce input voltages.

The glucose and insulin output signals

from the voltage comparator can be used to actuate corresponding electrically actuated fluid valves 90 and 92, respectively. These valves control, respectively, the flow of glucose and insulin from corresponding reservoirs 94 and 96 to the monitored living body, thus providing a fully closed loop system. Obviously, the insulin and the glucose reservoir and dispensing system can also be placed inside the living body with the amplified signal of the fuel cell glucose sensor feeding directly to the voltage comparitor to actuate the appropriate fluid valves.

It is well known that in an electrochemical sensing device, the activity of the platinized surface will degrade in time, resulting in a decrease in sensitivity and reproducibility of the hignal output. The electrode catalyst of the present glucose sensor can be rejuvenated to maintain its activity so as to eliminate or to reduce the frequency of recalibration after implantation. The rejuvenation is achieved by the use of a short duration cycle of negative and positive potential pulses to maintain a highly active, oxide-free fuel anode.

In the operation of the fuel cell glucose sensor, the platinum surface of the anode may slowly degrade by the external oxidation of the surface. These oxides inhibit the glucose oxidation reaction and decrease the available surface sites on the anode active toward the oxidation of aldchyde glucose. Also, if oxides are present on the surface of the anode, a fraction of the glucose presented to the anode for oxidation will be consumed in the chemical reduction of the oxide film, so that the total amount of glucose present will not be sensed by the anode since no electrons are donated to the anode in the chemical oxide reduction process.

This problem is eliminated by frequently actuating the platinized electrode by an electrochemical pulsing technique such as described in U.S. Patent No. 3,509,034, issued April 28, 1970 for Pulse-Activated Polarographic Hydrogen Detector. The anode is cycled from anodic to cathodic, going from oxygen evolution to hydrogen evolution, by means of a third biased electrode (not shown). The potential pulses are short-duration square waves generated at 20 second intervals. The anodic-cathodic polarization cycle is carried out about three times and is always terminated on the cathodic part of the cycle thereby reducing the platinum oxide surface to a highly active, disordered surface of platinum.

It will be appreciated from the preceding description that the glucose monitor and sensor of the present invention provides an accurate means for determining glucose levels in vivo, either by direct implantation or by subcutaneous insertions or in vitro.

Having described in detail a preferred embodiment of our invention, it will be apparent to those skilled in the art that numerous modifications can be made therein without departing from the scope of the invention as defined in the following claims.

WHAT WE CLAIM IS:—

1. A method for monitoring blood glucose levels comprising the steps of:—

(1) exposing a glucose diffusion-limited fuel cell as herein defined to the body fluid of a living body in such a way that a change takes place in the fuel cell in a selected characteristic that varies in a manner proportional to the blood glucose level and

(2) measuring the change in the selected characteristic or in a signal derived from the selected characteristic in order to obtain a measurement of the blood glucose level.

2. A method for monitoring blood glucose levels comprising the steps of:

(1) exposing a glucose diffusion-limited fuel cell as herein defined to the body fluid of a living body and

(2) converting the output current generated by said fuel cell into an electrical signal having a characteristic which varies in accordance with the magnitude of the output current, said output current magnitude being proportional to the blood glucose level in said living body.

3. A method according to claim 2 further characterized by actuating an alarm signal whenever the said electrical signal characteristic departs from a predetermined condition.

4. A glucose diffusion-limited fuel cell as herein defined comprising:—

(1) at least one permeable membrane which defines a chamber and which is permeable to body water, oxygen and glucose,

(2) first and second, spaced, catalyst-coated electrodes positioned within the chamber and comprising, respectively, a cathode electrode, and an anode electrode for said fuel cell,

(3) means for glucose diffusion limiting the said fuel cell,

(4) a load resistance electrically interconnected with the cathode and the anode electrodes and,

(5) an electrolyte interposed between the said first and second electrodes.

5. A fuel cell according to claim 4 wherein the anode has a smaller surface area than the cathode.

6. A fuel cell according to claim 4 or 5 wherein the anode includes means for impeding the diffusion of glucose.

7. A fuel cell according to claim 4, 5 or 6 wherein the cathode includes means for impeding the diffusion of glucose while permitting substantially free passage to water, ions, and oxygen whereby the cathode serves as an oxygen electrode.

8. A fuel cell according to any of claims 4 to 7 wherein said cathode and anode comprises dissimilar materials.

9. A fuel cell according to any of claims 4 to 8 wherein said anode catalyst is platinum.

10. A fuel cell according to any of claims 4 to 8 wherein said cathode catalyst is platinum.

11. An in vivo blood glucose level monitoring system comprising:

(1) a glucose diffusion-limited fuel cell as herein defined adapted for implantation in a living body, and,

(2) means for converting the output current generated by the fuel cell when implanted in a living body, into an electrical signal having a characteristic which varies in accordance with the magnitude of the output current, the said output current magnitude being a function of the blood glucose level in the living body.

12. A monitoring system according to claim 11 further characterized by alarm signal generating means responsive to the electrical signal characteristic for generating an alarm signal whenever the said characteristic departs from a predetermined condition.

13. A monitoring system according to claim 12 further characterized by:—

(1) means adapted when the system is in operation for generating a glucose valve actuation signal whenever the electrical signal characteristic departs in one direction from the said predetermined condition and an insulin valve actuation signal whenever the said characteristic departs in the opposite direction from the said predetermined condition;

(2) first fluid valve means adapted to respond to the glucose valve actuation signal,

(3) second fluid valve means adapted to respond to the insulin valve actuation signal,

(4) a source of glucose adapted to be fluidly coupled through the first valve means to the living body; and,

(5) a source of insulin adapted to be fluidly coupled through the second valve means to the living body.

14. A monitoring system according to claim 11 wherein the fuel cell comprises:—

(1) at least one permeable membrane which defines a chamber and which is permeable to body water, oxygen, and glucose,

(2) first and second spaced catalyst coated electrodes positioned within the chamber and comprising, respectively, a cathode electrode and an anode electrode for the fuel cell;

(3) means for glucose diffusion-limiting the fuel cell and,

(4) a load resistance electrically interconnected with the cathode and anode electrodes.

15. A monitoring system according to claim 11 further characterized by:—

(1) means adapted when the system is in operation for generating an insulin valve actuation signal whenever the electrical signal characteristic departs in one direction from the predetermined condition,

(2) fluid valve means adapted to respond to the insulin valve actuation signal and,

(3) a source of insulin adapted to be fluidly coupled through the fluid valve means to the living body.

16. A method according to claim 1 for monitoring blood glucose levels substantially as hereinbefore described.

17. A glucose diffusion-limited fuel cell as herein defined substantially as hereinbefore described with reference to the accompanying drawings.

18. An invivo blood glucose level monitoring system according to claim 11 substantially as hereinbefore described with reference to the accompanying drawings.

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1394171 COMPLETE SPECIFICATION
2 SHEETS *This drawing is a reproduction of the Original on a reduced scale*
Sheet 1

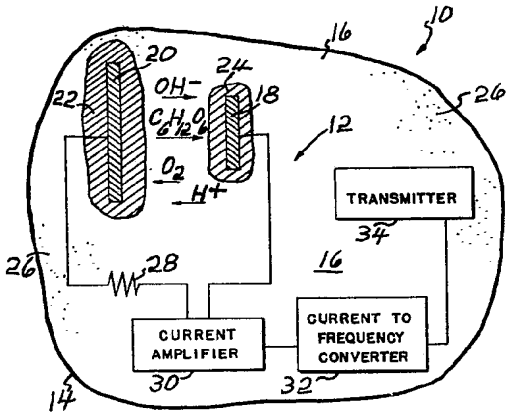
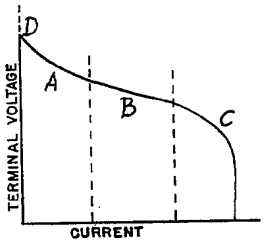


FIG. 1



A. ACTIVATION POLARIZATION
B. OHMIC POLARIZATION
C. CONCENTRATION POLARIZATION
D. OPEN CIRCUIT VOLTAGE

FIG. 2

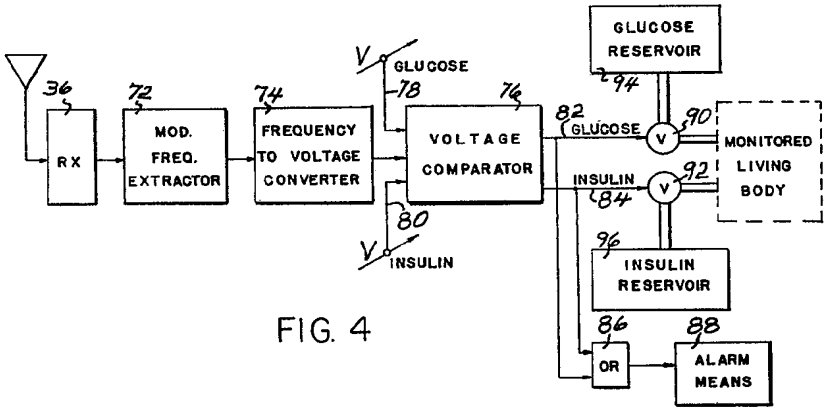


FIG. 4

1394171 COMPLETE SPECIFICATION
2 SHEETS This drawing is a reproduction of the Original on a reduced scale
Sheet 2

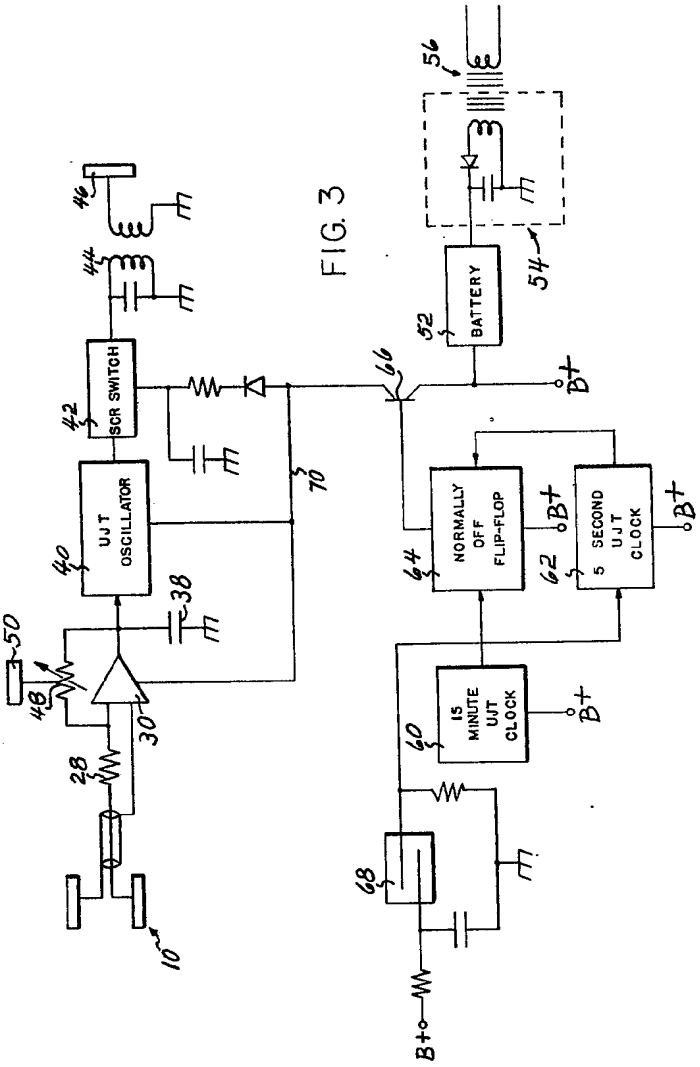


FIG. 3